

**UNITED STATES DISTRICT COURT  
DISTRICT OF MASSACHUSETTS**

**SERONO, INC.**

**Plaintiff**

**v.**

**FERRING PHARMACEUTICALS, INC.**

**Defendant**

Civil Action No. 02-11832MLW

**PLAINTIFF SERONO, INC.'S  
OPENING CLAIM CONSTRUCTION BRIEF**

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**I. INTRODUCTION**

Plaintiff Serono, Inc. (“Serono”) charges that Ferring Pharmaceuticals, Inc. (“Ferring”) is selling its Bravelle<sup>®</sup> FSH<sup>1</sup> formulation and is providing its customers with instructions for using the Bravelle<sup>®</sup> product in a manner which infringes the patents-in-suit. Specifically, Serono charges that Ferring has induced customers to administer the Bravelle<sup>®</sup> FSH product in a manner that infringes at least claims 1 and 3 of U.S. Pat. No. 4,589,402 (“the ‘402 patent”) (Exhibit 1) and at least claims 1, 2, 8, 9, 13, 14 and 16 of U.S. Pat. No. 4,845,077 (“the ‘077 patent”) (Exhibit 2).

The ‘402 and ‘077 patents reflect important discoveries for treating human infertility, including improved techniques for *in vitro* fertilization (“IVF”) and ovulation induction. Both patents date back to 1984, a time when these fertility techniques were still being pioneered. The first baby born anywhere using IVF was born in the U.K. during 1978, only six years earlier. The patents-in-suit disclosed substantially improved treatment methods for clinical physicians using Serono’s then-newly-developed FSH product, trade named “Metrodin<sup>®</sup>.” This newly developed FSH product was commonly referenced in the art as “pure” FSH; it was the first in a new category of FSH products known as “Urofollitropin.”<sup>2</sup>

Prior to Serono’s development of the “pure” FSH product, the state of the art product for ovulation induction and *in vitro* fertilization was a mixture of gonadotropin hormones purified from the urine of post-menopausal women.<sup>3</sup> Such human menopausal gonadotropin (“HMG”)

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<sup>1</sup> “FSH” is the common shorthand for a hormone named Follicle Stimulating Hormone.

<sup>2</sup> Ferring’s Bravelle<sup>®</sup> product is also a Urofollitropin. In fact, the full formal name of Ferring’s product is Bravelle<sup>®</sup> (Urofollitropin for injection, purified).

<sup>3</sup> The urine of post-menopausal women was used because, after menopause, women secrete these hormones in substantially larger amounts.

products comprised a mixture of two active ingredient hormones. More specifically, HMG products comprised (and still comprise) roughly equal amounts of FSH and LH (“Luteinizing Hormone”), together with large amounts of other urinary by-products.

As of the time of the invention, clinicians knew that both FSH and LH had complex roles in human fertility. The ovaries contain follicles, which in turn contain ova, *i.e.*, immature eggs. The follicles hold the eggs during the maturation process. Upon maturation, the follicles burst open and the eggs are released during the process known as ovulation. This overall process results from a complex interacting cascade of multiple hormones, which include feedback checks and balances. At the time of the invention, clinicians knew that both FSH and LH played important roles in the overall process, but many important details of those roles were unknown.

Dr. Hodgen and his co-inventors were the first to develop infertility treatment regimens using “pure” FSH. Dr. Hodgen had confirmed that Serono’s “pure” FSH had no detectable LH activity using then-available biological activity tests, *i.e.*, an *in vitro* bioassay. The use of FSH alone, without any LH bioactivity, flew in the face of the prevailing thought among clinicians. “Since both hormones [were] known to be necessary, it is dogma that administration of . . . gonadotropins requires the co-joint administration of FSH and LH.” ‘402 Patent File History, Amendment Under Rule 115, October 14, 1985 (Amendment A) (Exhibit 3). This invention was the subject matter of the ‘402 patent.

In a related invention, Dr. Hodgen discovered additional benefits from adding another type of compound, a Gonadotropin Releasing Hormone antagonist (“GnRH antagonist”), in connection with infertility treatment. As described in more detail below, he found that the administration of GnRH antagonist indirectly reduced the estrogen variability that otherwise occurred in female patients during fertility treatments. By adding a GnRH antagonist to the treatment, externally administered (“exogenous”) hormones, such as FSH and LH, would play a

more controlled role in follicle maturation and ovulation. With this invention, the clinician was better able to regulate the total levels of FSH and LH in the patient during treatment; thus, the clinician was thereby better able to prevent a premature LH surge which might induce a poorly timed ovulation. This use of GnRH antagonist became the subject matter of the '077 patent.

## **II. CLAIM TERMS/PHRASES FOR CONSTRUCTION**

The following claim terms may be disputed,<sup>4</sup> and thus subject to claim construction:

- “exogenous human menopausal gonadotropin” (both patents, all asserted claims);
- “employing FSH . . . in the absence of exogenous LH” ('077 patent, claim 1) and “employing FSH alone . . . without the presence of exogenous LH” ('402 patent, claim 1);
- “gonadotropin releasing hormone antagonist” ('077 patent, claim 1 and 13);
- “in an amount sufficient to suppress the endogeneous FSH and LH secretion of said female” ('077 patent, claim 1 and 13);
- “cojointly with said FSH” ('077 patent, claims 1 and 13); and
- “wherein an ovulatory inducing amount of hCG is given.” ('402 patent, Claim 3).

## **III. BACKGROUND**

The inventions described in the '402 and '077 patents arose out of research performed at the Eastern Virginia Medical School by Dr. Gary Hodgen, Dr. Howard Jones, and Dr. Georgeanna Jones. Both patents were part of the early research efforts by pioneers in treating female infertility, including advancements in IVF and ovulation induction techniques.

Infertility is defined by the World Health Organization (WHO) as the inability of a couple to achieve conception or bring a pregnancy to term after one year or more of regular,

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<sup>4</sup> The Joint Scheduling Order indicated each party's claim construction statement should identify the terms the party contends need to be construed, along with the party's proposed definition of such terms. Ferring's claim construction statement included every term of every asserted patent claim. Nonetheless, it appears there is no dispute as to many of the claim terms.

unprotected sexual intercourse. At least 10% of couples worldwide are unable to conceive a child, and a further 10 - 25% of couples worldwide are unable to conceive a second or subsequent child, *i.e.*, secondary infertility. Using techniques pioneered by the inventors, infertility therapy is now highly successful.

**A. Basic Background Regarding Female Hormones and Ovulation**

The menstrual cycle is regulated by a cascade of female hormones. Some of these hormones are known as gonadotropins, as they support the function of the gonads, such as the ovaries in women. An ovary has a large number of eggs, each egg being contained in a “follicle,” which is a collection of small round cells enclosing the egg within the ovary. As follicles develop, they begin to grow along with the enclosed egg. Once the follicle fully develops and the egg matures, the follicle bursts and the egg is released, resulting in the process known as “ovulation.”

In normal follicular maturation, many follicles may begin development, but usually only one is destined to ovulate. This one is known as the “dominant follicle.” Once the dominant follicle ruptures and the egg is released, the other developing follicles fall into a state of atresia or death.

At the time of the inventions<sup>5</sup>, the complex roles of FSH and LH in the development of follicles and maturation of eggs resulting in ovulation were still being determined. A different hormone, known as Gonadotropin Releasing Hormone (“GnRH”), was known to stimulate the pituitary gland to release the gonadotropin hormones, FSH and LH. *See* `077 Patent, col. 1, line 66 – col. 2, line 6; `077 Patent File History, Amendment Under Rule 115 dated Oct. 22, 1984, p. 2-3 (Exhibit 4). *See also* Taber’s Cyclopedic Medical Dictionary (“the releasing hormone

produced in the hypothalamus. It acts on the pituitary to cause release of the gonadotrophic hormones”) (Exhibit 5). During early fertility treatments, FSH and LH were typically administered together in an HMG product.

Estrogen plays multiple, sometimes contradictory, roles in ovulation. As follicles grow, they produce estrogen, which stimulates development of the uterine lining. Estrogen also signals back to the hypothalamus to reduce the levels of GnRH, which in turn limits the pituitary’s production of FSH and LH, thus reducing stimulation of the ovary and stunting the development of the non-dominant follicles. Conversely, when estrogen production reaches a critical level, the pituitary gland releases a surge of LH. ’077 patent, col. 1, lines 51-57. In the normal cycle, this LH surge provides a final push to maturation of the egg in the dominant follicle and, within about 36 hours, ovulation occurs, *i.e.*, the egg is released from the follicle. ’077 patent, col. 1, lines 24-26.

Variations in endogenous estrogen levels in women create unpredictability for the timing of the LH surge that induces maturation of the egg. ’077 patent, col. 2, lines 10-14. If uncontrolled, the LH surge can occur either too late or too early for optimized IVF procedures. To prevent the LH surge from occurring too late, clinicians began using another hormone, “human Chorionic Gonadotropin” (or “hCG”). This hormone was used to mimic the LH surge, thereby allowing the clinician to induce maturation of the egg at a predetermined time. ’077 patent, col. 2, lines 13-16. However, spontaneous LH surges could still occur prematurely, thus preventing an effective IVF procedure. *Id.* at lines 16-18. As described in more detail below, the ’077 patent addresses the problem of premature maturation and ovulation.

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<sup>5</sup> The applications for the two inventions were filed in 1984 just a few months apart. The ’077 patent application was filed in April 1984, and the ’402 patent application was filed in July 1984.

At a basic level, the functions of these hormones were known to be as follows:

- FSH (Follicle Stimulating Hormone) – when administered in a mixture with LH, it stimulates follicles and eggs to grow.
- LH (Luteinizing Hormone) – helps with hormone production and causes final maturation of the egg and its release from the follicle (ovulation).
- hCG (Human Chorionic Gonadotropin) – a hormone normally secreted by the placenta to support continued progesterone production to maintain the uterine lining. hCG is also used as a treatment to mimic the LH surge in IVF. '042 patent, col. 1, lines 42-46.
- Estrogens – hormones produced by the ovary; cause the uterine lining to grow; an increase usually causes a reduction of FSH and LH production but, at high levels, results in the LH surge. '077 patent, col. 1, lines 55-57.
- Progesterone – a hormone that is secreted after ovulation - further differentiates the uterine lining to prepare it for an embryo.
- GnRH (Gonadotropin Releasing Hormone) – stimulates the pituitary to secrete FSH and LH gonadotropins. '077 patent, col. 1, line 66 – col. 2, line 6. It works by binding a receptor on cells in the pituitary. *See* '077 Patent File History, Amendment Under Rule 115, dated Oct. 22, 1984, p. 2-3.

**B. IVF and Ovulation Induction Before the Claimed Inventions**

The term “ovulation induction” (“OI”) refers to a particular infertility treatment, *i.e.*, inducing ovulation in females by administering fertility hormones according to a specified regimen. OI is typically practiced in connection with natural insemination to achieve fertilization. *In vitro* fertilization (“IVF”), by contrast, involves inducing maturation of follicles, followed by harvesting eggs before ovulation, inspection and fertilization of eggs outside the body, and re-implantation of selected fertilized eggs.

Throughout the 1970's and early 1980's, the standard techniques for OI and IVF relied upon “Human Menopausal Gonadotropins” (“HMG”) to stimulate the growth of follicles. As noted above (Section I, p. 1), HMG was a mixture of FSH and LH extracted from the urine of postmenopausal women. There were two basic reasons for the use of the HMG combination of FSH and LH: first, prevailing wisdom at the time was that LH was necessary for the process to

be successful; and, second, it was very difficult to completely separate FSH and LH because the two molecules are structurally very similar.

In sum, fertility treatments of that time used HMG to induce maturation of the follicle and hCG to mimic an LH surge for release of the egg. These techniques had proved effective to some degree, but the process was “notoriously difficult to manage” and was widely seen as lacking uniform success. ‘402 patent, col. 2, lines 49-54. For this reason, members of the infertility community – most prominently those associated with Serono – sought to develop a “pure” FSH formulation for clinical use.

### C. The Advent of “Pure” FSH

At the time of the present inventions, the state of the art for “pure” FSH for clinical use was Serono’s Metrodin® product, also known as “Urofollotropin”.<sup>6</sup> Metrodin® was a “pure” FSH compound that contained no detectable LH bioactivity, *i.e.*, the level of LH was undetectable based on then-available 1984 bioassay technology. This background fact is widely reflected in the contemporaneous literature of that time:

Exogenous gonadotropins were either “pure” FSH (Metrodin or Urofollotropin, Serono Laboratories, Inc. Randolph, MA) or hMG (Pergonal, Serono). The “pure” FSH was in vials containing 25 IU FSH. Using an in vitro bioassay, LH was undetectable (<40 mIU/ml – Serono International Reference Preparation – or <10 ng/ml) in the pure FSH preparation, confirming earlier findings.

Kenigsberg *et al.*, *Dose response using a gonadotropin releasing hormone antagonist*, 42 Fertil. & Steril., No. 1, pp. 116-26 (July 1984) (emphasis added) (Exhibit 6).

Counting the first day of spontaneous menses as cycle day 1, monkeys were treated with 25 IU (intramuscularly) of “pure” FSH (Urofollotropin, Serono Laboratories, Inc. Randolph, MA) twice daily (A.M. and P.M.) according to these regimens . . . .

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<sup>6</sup> Urofollitropin actually refers to a category of products but, at that time, Serono’s Metrodin® was the only existing product in that category.

Schenken *et al.*, *Ovulation induction using "pure" follicle-stimulating hormone in monkeys*, 41 Fertil. & Steril. No. 4, 629-34 (April 1984) (emphasis added)(Exhibit 7).

This "pure" FSH – Urofollotropin, or Metrodin® – was understood by those of skill in the art to be "FSH alone," without LH. The same Schenken *et al.* article states at page 633:

Interestingly, FSH treatment at supraphysiologic levels stimulated the maturation of apparently competent follicles, without exogenous LH. Our findings imply that when FSH (alone) is administered to enhance the natural ovarian cycle, the concurrent [endogenous] LH secretion may be sufficient until the midcycle surge.

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[T]his report established that FSH alone may be useful for situation of the natural ovarian cycle.

**D. The Inventions Described and Claimed In The Patents In Suit**

At the same time Serono began making Metrodin® available, clinicians were learning more about how hormones work in female fertility, and they were developing new regimens for improving OI and IVF treatments. The '402 and '077 patents are directed to different methods of improving these various regimens developed by Dr. Gary Hodgen and his colleagues.

**1. The '402 patent**

With Serono's new biologically pure FSH product, Metrodin®, clinicians were able to test certain theretofore scientifically accepted notions. As of the early 1980's, it was then accepted dogma that some LH was necessary to induce follicular growth, and therefore that administration of at least some LH in connection with FSH was necessary for OI and IVF. '402 Patent File History, Amendment Under Rule 115, October 15, 1985 (Amendment A), pp. 1-2 ("Since both hormones are known to be necessary, it is dogma that administration of endogenous gonadotropins requires the co-joint administration of FSH and LH.") (Exhibit 3).

The inventors of the '402 patent discovered that belief was not true. Exogenous LH did not have to be administered; rather, administering FSH containing no detectable LH bioactivity achieved fertility at least as well as the co-administration of FSH and LH. '402 patent, col. 4, lines 22-29. Indeed, pure FSH therapy was just as effective as HMG in maintaining an increased number of viable follicles in normal women. '402 patent, col. 5, lines 28-33. However, the use of the Urofollitropin, *i.e.*, pure FSH with no detectable LH bioactivity, provided a significant increase in the resulting number of successful pregnancies. '402 patent, col. 6, lines 4-10.

## 2. The '077 patent

As described in the specification of the '077 patent, the variability of estrogen levels of individual women during human menopausal gonadotropin therapy is highly problematic to fertility treatment. '077 patent, col. 4, lines 10-14. Variable levels of endogenous estrogen influence the production of variable levels of endogenous FSH and LH. The effect on LH levels is particularly important. Variable estrogen levels can result in an unpredictable LH surge, causing either premature or belated ovulation.

According to the invention, a GnRH antagonist will bind to the GnRH receptor without evoking secretion of FSH and LH. Thus, administration of the GnRH antagonist suppresses the normal secretion of FSH and LH in the ordinary menstrual cycle, regardless of estrogen variability, and better allows the clinician to carefully control the timing of follicle maturation. *See* '077 Patent File History, Amendment Under Rule 115, dated Oct. 22, 1984, (Amendment A), p. 2 (Exhibit 4).

As such, the clinician can administer "pure" FSH (*e.g.*, Serono's Metrodin<sup>®</sup> product), or HMG (*i.e.*, a mixture of exogenous FSH and LH), or a combination of the two, without interference from endogenous estrogen causing a premature LH surge. *See, e.g.*, '077 Patent File History, Response to Final Rejection, dated May 28, 1985 (Amendment B), p.5 ("Applicant